

## **REMARKS**

Following entry of the foregoing amendments, claims 4, 5, 34, 37, 38, 49, 50, 53 to 63, 72, 74 to 78, 94 to 96, 104, and 105 will be pending in this patent application. Claims 4, 5, and 34 have been amended, and claims 6, 7, 46, 51, and 65 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. For example, support for the amendments to claim 34 is found in paragraphs 27 and 89. The amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

### **Alleged Obviousness**

Claims 4 to 7, 34, 37, 38, 46, 49 to 51, 53 to 63, 65, 72, 74 to 78, 94 to 96, 104, and 105 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888 (“the Elbashir article”); published U.S. patent application number U.S. 2003/0143732 (“the Fosnaugh application”); and published U.S. patent application number U.S. 2003/0206887 (“the Morrissey application”) in view of the combined teachings of U.S. patent number 6,262,036 (“the Arnold patent”); published U.S. patent application number U.S. 2005/0142535 (“the Damha application”); and U.S. patent number 6,133,246 (“the McKay patent”). Applicants respectfully request reconsideration and withdrawal of the rejection because the presently claimed compositions would not have been obvious to those of ordinary skill in the art at the time of the invention.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). The Patent Office must also identify “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex*, 127 S.Ct. 1727,

1741. In other words, the Office must identify “an apparent reason to combine the known elements *in the fashion claimed by the patent at issue*. To facilitate review, this analysis should be made explicit.” *KSR Int’l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006)).

The claims as amended recite compositions that comprise two chemically synthesized oligomeric compounds in which at least one of the oligomeric compounds comprises ribonucleosides having 2’-F or 2’-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub> substituent groups that alternate with β-D-deoxyribonucleosides. The Elbashir article, the Fosnaugh and Morrissey applications, the Arnold patent, the Damha application, and the McKay patent fail to teach or suggest first and second oligomeric compounds having this particular pattern of chemical modifications. Instead, the references merely provide generalized teachings regarding chemical modification of RNA or describe oligomeric compounds that have patterns of chemical modifications that differ significantly from the pattern claimed.

For example, the Elbashir article describes chemically modified siRNA duplexes in which one or both of the siRNA strands is fully substituted with 2’-deoxynucleotides or with 2’-O-methyl-containing nucleotides.<sup>1</sup> The article also describes modified siRNA duplexes in which either the two nucleotide overhangs at the 3’ ends of the duplexes or the four terminal nucleotides at the 3’ ends of the duplexes are substituted with 2’-deoxynucleotides.<sup>2</sup> The article reports that the fully modified siRNA molecules exhibited no activity, while the activity of the 3’-substituted siRNAs was not affected by the chemical modifications.<sup>3</sup>

The Fosnaugh application merely provides generalized teachings regarding chemical modification of RNA. The application provides a broad listing of possible chemical modifications for oligomeric compounds and states that such modifications can be incorporated into siRNA molecules.<sup>4</sup>

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<sup>1</sup> Paragraph spanning pages 6681 to 6682.

<sup>2</sup> *Id.*

<sup>3</sup> *Id.*

<sup>4</sup> Paragraph 39.

The Morrissey application describes chemically-modified siRNA molecules that target hepatitis B virus. The application provides a general description of various possible 2' modifications and states that such modifications can be introduced into the described siRNA molecules.<sup>5</sup> Significantly, the application teaches that the 2' modifications can be placed at either the 3' or 5' ends of the siRNA molecules or at internal pyrimidine-containing nucleotides.<sup>6</sup>

The Arnold patent describes antisense oligonucleotides that contain alternating modified internucleoside linkages. Example 34 of the patent describes a series of oligomers that contain alternating and mixed internucleoside linkages (methylphosphonate, phosphorothioate and phosphodiester) and have identical 2' groups that are either all 2'-H or 2'-O-methyl.

Although the Damha application describes oligonucleosides containing sugar-modified nucleosides that alternate with 2'-deoxynucleosides, the application fails to teach or suggest siRNA molecules comprised of such oligonucleosides, as pointed out the by the Office.<sup>7</sup>

The McKay patent describes chimeric oligomeric compounds such as gapmers and wingmers that comprise two or more chemically distinct regions.<sup>8</sup> The patent does not teach that such chimeric oligomeric compounds include 2'-substituted ribonucleosides that alternate with 2'-deoxyribonucleosides.

The chemical modifications described in the Elbashir article, the Fosnaugh and Morrissey applications, the Arnold patent, the Damha application, and the McKay patent could be combined into a huge number of possible patterns of modifications that could be incorporated into siRNA molecules, and the references fail to provide any useful guidance regarding the particular patterns of modifications that should be incorporated into siRNA molecules to enhance the molecules' activities or properties. Significantly, the Arnold patent, the Damha application, and the McKay patent do not describe siRNA molecules, and, hence, do not provide guidance regarding *specific patterns of 2' chemical modifications* that those skilled in the art would have expected to enhance the activities or properties of siRNA molecules at the time of the invention.

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<sup>5</sup> Paragraphs 50, 58, and 59

<sup>6</sup> Paragraphs 59, 62, 94, 95, and figures 4 and 5

<sup>7</sup> Advisory action dated December 4, 2007, pages 3 to 4.

<sup>8</sup> Col. 11, lines 32 to 64 and Tables 11, 12, 14, 19, 21, 24, and 26.

Moreover, the references fail to teach or suggest that the particular pattern of chemical modifications recited in the claims would have been any more desirable or useful than any of the other possible patterns of chemical modifications encompassed by the references' descriptions of chemical modifications.

Similarly, the Elbashir article, and the Fosnaugh and Morrissey applications do not provide any guidance or detail regarding the particular types of chemical modifications, the number of chemical modifications, and the positioning of the chemical modifications within an siRNA molecule that would have been expected to impart beneficial properties to the molecule while still maintaining the molecule's activity. The appropriate way to design chemically modified siRNAs to impart enhanced properties to the molecules relative to unmodified molecules would thus have been unpredictable to those of ordinary skill in the art at the time of applicants' invention. Such artisans therefore would have had *no reason* to select the particular pattern of chemical modifications presently claimed from the thousands of possible patterns of chemical modifications encompassed by the cited references' teachings. In fact, the Fosnaugh and Morrissey applications actually teach away from the claimed pattern of chemical modifications by illustrating particular chemically modified siRNA molecules in Figures 4 and 5 that contain chemical modification patterns that are very different from those recited in the claims. Similarly, the Elbashir article also teaches away from the claimed pattern of chemical modifications by describing siRNA duplexes that contain chemical modifications at locations that also vary significantly from the pattern claimed and that do not enhance the molecules' activities or properties.

Those of ordinary skill in the art therefore would have had *no reason* to produce oligomeric compounds containing the claimed pattern of chemical modifications at the time of the invention due to the fact that nothing in the Elbashir article, the Fosnaugh and Morrissey applications, the Arnold patent, the Damha application, and the McKay patent, either alone or when considered together, teaches or suggests that the particular pattern of modifications claimed would have been expected to confer any particular advantage to siRNA molecules *relative to the advantageous properties said to be conferred by the thousands of other possible*

*combinations of chemical modifications encompassed by the descriptions provided in the references.* Accordingly, those of ordinary skill in the art thus would have had no reason to produce the claimed compounds.

Moreover, applicants have demonstrated that oligomeric compounds possessing the claimed pattern of chemical modifications are highly effective at inhibiting target RNA expression.<sup>9</sup> Nothing in the cited references teaches or suggests that oligomeric compounds bearing the particular pattern of chemical modifications recited in the claims would be so effective at inhibiting target RNA expression. That is, nothing in the references teaches or suggests that the particular type, number, and pattern of chemical modifications recited in the present claims would result in oligomeric compounds that are effective to reduce target RNA expression by 78 % to 91 %. The results described in Examples 2, 3, and 6 of the present application would thus have been completely unpredictable to those of ordinary skill in the art at the time of the invention.

There would have been no reason for those of ordinary skill in the art to design and produce oligomeric compounds possessing the particular pattern of chemical modifications recited in the claims upon review of the references cited by the Office at the time of the invention. The claimed oligomeric compounds therefore would not have been obvious to those of ordinary skill in the art, and applicants accordingly, respectfully, request withdrawal of the rejection.

### **Alleged Double Patenting**

Claims 4 to 7, 34, 37, 38, 46, 49 to 51, 53 to 63, 65, 72, 74 to 78, 94 to 96, 104, and 105 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 36, 40, 44, 46 to 49, 52 to 64, 74 to 80, 93, 98 to 100, and 104 of copending U.S. patent application number 10/860,265. In addition, claims 4 to 7, 34, 37, 38, 46, 49 to 51, 53 to 63, 65, 72, 74 to 78, 94 to 96, 104, and 105 have been independently provisionally rejected under the judicially created doctrine of obviousness-type

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<sup>9</sup> See examples 2, 3, and 6.

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double patenting as allegedly unpatentable over claims 1 to 24 of copending U.S. patent application number 11/054,848. Applicants respectfully request that these rejections be deferred pending the identification of allowable subject matter in the present application, as the rejections can likely be readily resolved, depending upon the subject matter ultimately allowed, through the filing of suitable terminal disclaimers.

### **Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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